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U.S. High Production Volume (HPV) Chemical Challenge Program

SUMMARY OF EXISTING DATA, PROPOSED TEST PLAN AND RATIONALE FOR COBALT SALTS OF C8 TO C13 CARBOXYLIC ACIDS INCLUDING NEODECANOIC ACID, COBALT SALT (CASRN 27253-31-2), FATTY ACIDS, C9-C13 NEO, COBALT SALTS (CASRN 68955-83-9) AND HEXANOIC ACID, 2-ETHYL, COBALT SALT (CASRN 136-52-7)

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on Behalf of the Sponsoring Companies:

OM Group, Inc., The Shepherd Chemical Company and Troy Corporation

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INTRODUCTION

The following document includes a test plan and a summary of existing data for the following HPV compounds:

- Hexanoic acid, 2-ethyl, cobalt salt [CASRN 136-52-7]
- Neodecanoic acid, cobalt salt [CASRN 27253-31-2]
- Fatty acids, C9-C13 neo, cobalt salts [CASRN 68955-83-9]

The information provided in this document and the attached dossier of robust summaries meets the requirements under the U.S. High Production Volume (HPV) Chemical Challenge. These three compounds are part of 19 sponsored chemicals organized under the Metal Carboxylates Coalition (The Coalition), an HPV testing consortium managed by the Synthetic Organic Chemical Manufacturers Association's (SOCMA) VISIONS Department. The Coalition member companies sponsoring these three compounds are OM Group, Inc., The Shepherd Chemical Company and Troy Corporation.

USE PATTERNS AND REGULATORY BACKGROUND

The three compounds in this category are closely related cobalt salts of carboxylic acids, and are all members of the metal carboxylates group. Hexanoic acid, 2-ethyl, cobalt salt is the cobalt salt of 2-ethylhexanoic acid, a C-8 carboxylic acid ($C_8H_{16}O_2$). Neodecanoic acid, cobalt salt is the cobalt salt of neodecanoic acid, a C-10 carboxylic acid ($C_{10}H_{20}O_2$). Fatty acids, C9-C13 neo, cobalt salts include cobalt salts of fatty acids, C9-C13 neo, which are C-9 to C-13 carboxylic acids.

The structures of hexanoic acid, 2-ethyl, cobalt salt and neodecanoic acid, cobalt salt are presented in Figures 1 and 2. The structure of fatty acids, C9-C13 neo, cobalt salts is variable, depending upon the number of carbon atoms.

Figure 1: Structure of hexanoic acid, 2-ethyl, cobalt salt

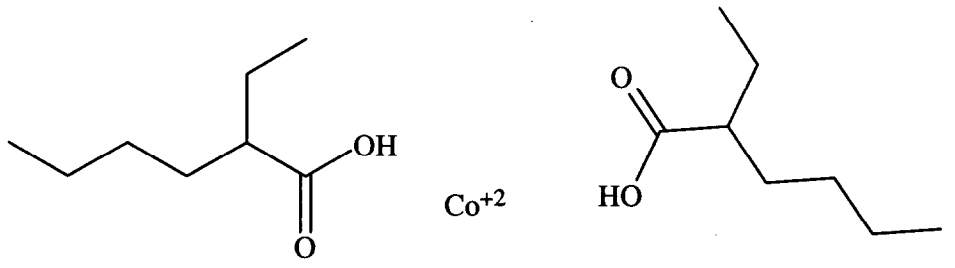
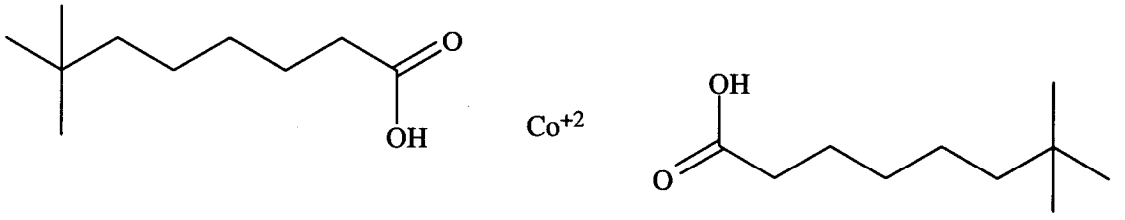


Figure 2: Structure of neodecanoic acid, cobalt salt



All of the metal carboxylate salts are designed to add metals to chemical reactions. They therefore are expected to dissociate into free metal and free acid.

In general the cobalt carboxylates are used as oxidative polymerization catalysts in many product areas. These areas include but are not limited to: ink and paint driers; unsaturated polyester resins, and hydrodesulfurization in their manufacturing; and the making of the insecticide DEET (diethyltoluamide). Some of these carboxylate compounds are used in oxygen scavenger plastics as well (for example, plastic bottles). The tire industry also uses cobalt carboxylates as adhesion promoters in tire manufacturing. These compounds facilitate adhesion between the rubber in the steel cords. The metal (not salt) loadings range from 0.01-0.5% depending upon the application listed above. Hexanoic acid, 2-ethyl, cobalt salt (also known as cobalt octoate or cobalt 2-ethylhexanoate) is used in paint driers, polyester initiators, and petrochemical catalysts. Neodecanoic acid,

cobalt salt (also known as cobalt neodecanoate) is used as a rubber adhesion promoter and plastic degradant.

One characteristic of these metal carboxylates is that they readily dissociate from an ion pair into free metal and free acid. They are found as partially dissociated products in the ambient environment (i.e., neutral pH). Dissociation is a reversible process and the proportion of dissociated salt is dependent on the pH and pKa (the dissociation constant), which is the pH at which 50% dissociation occurs. In the low pH environment of the digestive tract (e.g., pH 1.2) complete dissociation will occur for these metal carboxylates. The transport and bioavailability of the metals and acids are determined by their solubility in environmental media and biological fluids which is determined by environmental parameters such as pH.

Dissociation is a reversible reaction, splitting the parent compound into two or more chemical species which may be ionic, but are not necessarily so. The process can be generally represented as:

$$[RCOO^-]_x{:}[M^+] \xleftrightarrow{pK1} [RCOO^-]_x + [M^+] \xleftrightarrow{pK2} [RCOOH]_x + [M^+]$$

undissociated salt — **dissociated acid and metal** — **neutral species + ionized metal**

High pH — Low pH

The pKa and pH are equal when the metal carboxylate salt is 50% dissociated. The parent compounds, the metal carboxylate salts, are associated ionized molecules.

The relevant dissociation products for each of the three chemicals are as follows:

- For hexanoic acid, 2-ethyl, cobalt salt: 2-ethylhexanoic acid and cobalt chloride
- For neodecanoic acid, cobalt salt: neodecanoic acid and cobalt chloride
- For fatty acids, C9-C13 neo, cobalt salts: fatty acids, C9-C13, neo and cobalt chloride

The Metal Carboxylates Coalition conducted studies following OECD Guideline 112 to determine the dissociation constant of each of the three chemicals. The mean pKa values at 20ºC were as follows:

- Hexanoic acid, 2-ethyl, cobalt salt: 6.41
- Neodecanoic acid, cobalt salt: 6.52
- Fatty acids, C9-C13 neo, cobalt salts: 5.96

These results indicate that a moderate amount of dissociation will occur at approximately neutral pH (i.e., representative of aquatic and marine ecosystems), while complete dissociation will occur at the physiologically relevant pH of the

mammalian stomach (pH 1.2). These findings are particularly important in relating available data for the dissociation products to support the existing data for the metal carboxylate salts in the fulfillment of critical endpoints.

Because the free acid (2-ethylhexanoic acid, neodecanoic acid, or fatty acids, C9-C13 neo) and corresponding free metal (cobalt) have different characteristics (e.g., solubility, adsorption, and toxicity) than does the undissociated salt (ion pair), the proportion of dissociation influences the behavior of the substance in the environment and *in vivo*. The bioavailable fraction of the constituents of metal carboxylate salts can be estimated from the dissociation constants.

There are two principal hazard assessments being evaluated based on the current data for the three chemicals in this category. The first is the hazard to aquatic organisms due to environmental exposure. The second is hazard to mammalian systems as a result of oral exposure. Based upon the range of pKa values (5.96 to 6.52), it is expected that in the ambient aquatic environment, moderate portions of each of these chemicals will be dissociated; therefore, part of each compound will be present as the respective acid and cobalt cations. In the environment (i.e., aquatic systems), toxicity is typically related to the free metal ion concentration (U.S. EPA, 2002). The metal ion pair (salt) is less likely to be absorbed and to contribute to toxicity.

At the low pH of the mammalian stomach (pH 1.2) all of the metal carboxylates, including the three chemicals in this category, are expected to be completely, or nearly completely, dissociated. This indicates that when administered orally, the absorption and resulting toxicity would be due to the independent action of the respective acid and the free (ionized) cobalt. This is supported by *in vivo* and *in vitro* data with cobalt acetate and other cobalt containing carboxylates (Firriolo 1992.; Speijers et al 1985; Stopford et al. 2003) (See discussion below).

The dissociation constants show that at the pH of the stomach, the important moieties from a toxicological standpoint are the unionized free acid and ionized cobalt. Because of this dissociation in the stomach, mammalian toxicity data for the three acids (2-ethylhexanoic acid, neodecanoic acid, and fatty acids, C9-C13 neo) can serve as a surrogate data for the carboxylic acid component of the three compounds (hexanoic acid, 2-ethyl, cobalt salt; neodecanoic acid, cobalt salt; fatty acids, C9-C13 neo, cobalt salts), respectively. Similarly, under these conditions, data for cobalt can be represented by fate and toxicity data for free ion or simple metal salts (e.g., cobalt chloride). Therefore, the role in any observed toxicity for acids and metals can be evaluated independently. The combination of the acid and the metal can be used to supplement the characterization of toxicity of the salt and support a read across as part of the category strategy to determine needs for additional data.

Bioequivalency

The work described below by Stopford et al. (2003) shows that cobalt chloride is similar to, or more bioavailable than, the corresponding cobalt carboxylate salts, which makes the chloride a conservative surrogate in estimating bioavailability and toxicity of dissociated metal. Cobalt chloride has thus been emphasized during preparation of the attached robust summaries and provides the preferred surrogate data for cobalt carboxylate salts, including the three in this category.

The recent studies by Stopford et al. to evaluate the "bioequivalency" (an estimate of bioavailability) of cobalt compounds included three cobalt carboxylates and cobalt chloride (when added as fine powders) in synthetic fluids designed as surrogate gastric juices. These investigators showed that these cobalt salts were completely dissociated and dissolved at a gastric pH (1.2) (Table 1). When added to surrogate intestinal fluids at neutral pH (7.4), $Co(II)Cl_2$ was also highly soluble. The solubility of the cobalt (% available cobalt expressed as Co(II) ion) in cobalt carboxylates ranged from 30.8 to 50.8 percent available cobalt at 72 hours (Table 1). These results for cobalt chloride and cobalt naphthenate are highly consistent with data reported by Firriolo (1992) for these same salts in similar surrogate biological fluid matrix (Table 1). Maximum solubility of Co naphthenate was observed at 48 hrs, which was the longest sample time used in the study.

These bioequivalency data are valuable for two reasons. They confirm the prediction from the dissociation studies that these compounds are expected to be completely dissociated in the gastrointestinal tract (low pH) and a substantial proportion of these compounds would be expected to be dissociated and bioavailable in water at neutral pH (7.4).

Table 1: Results of extraction of cobalt from surrogate biological fluids

Matrix (pH)	**Maximum Solubility (% of available metal)**			
	$CoCl_2$	Co 2-ethyl-hexanoate	Co naphthenate	Co neodecanoate
Gastric pH (1.5)[a]	100	100	100	100
Gastric pH (2.0)[b]	100		100	--
Intestinal pH (7.4)[a]	100	50.8*	45.4*	30.8*
Intestinal pH (7.3)[b]	85	--	20**	--

[a] From Stopford et al. (2003); [b] Firriolo (1992)

* Maximum concentration observed at 72 hours.

** Maximum concentration observed at 48 hours.

Stopford et al. (2003) and Firriolo (1992) added all of the salts to the neutral (intestinal) surrogate solutions as finely ground powder. It is not surprising that the percent of available cobalt from cobalt carboxylates appears to increase with time (48 or 72 hours). Firriolo (1992) also evaluated the solubility of ground and

ethanol-solubilized cobalt naphthenate in a neutral buffer solution[1]. For ground cobalt naphthenate, 20% of available Co(II) was dissociated. In contrast, 90% of available cobalt was observed as dissociated Co(II) when originally introduced in ethanol. The ethanol-solubilized Co(II) remained in solution. This finding has implications for dissociated Co(II) introduced to the intestine solubilized in gastric juices.

Cobalt is absorbed primarily as the free Co(II) ion via biochemical mechanisms at the intestinal mucosal wall (Firriolo 1992). Having been reported as completely soluble in gastric fluids (Stopford et al. 2003; Firriolo 1992), Co(II) should remain soluble (100% dissociated Co(II)) after entering the intestine from the stomach. Once solubilized, this cobalt would be expected to undergo the same fate irrespective of the salt originally ingested. Stopford et al. (2003) emphasized the importance of confirming the interpretation of *in vitro* solubilities in surrogate fluids with *in vivo* data. In fact, Firriolo used these (Table 1) *in vitro* solubility tests as preliminary studies for subsequent comparative absorption, distribution and elimination studies. Discussion of *in vivo* data is presented in the following section.

Finally, the work by Stopford et al. (2003) shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts (Table 1), which makes the chloride a conservative surrogate when attempting to estimate the bioavailability and toxicity of dissociated metal salts. For this reason, data for the chlorides of cobalt have been emphasized during preparation of the attached robust summaries and is the preferred surrogate for the cobalt dissociation product of each of the three compounds.

Comparative Toxicity and Pharmacokinetics

Toxicity data for soluble cobalt salts indicate that the contribution of the respective anion to the toxicity of the compound is negligible compared with that of the cobalt cation. Speijers et al. (1982) investigated the acute oral toxicity in rats of a series of cobalt compounds including cobalt acetate. Lethal doses varied significantly when calculated in terms of the compound weight; however, when based on the dose of the Co(II) ion, all of the LD50 values were within a factor of about two for all of the compounds (Table 2). With the exception of the fluoride and bromide salts, all other salts tested had LD50 values within the range from 140 to 190 mg Co/kg bw. The LD50 for cobalt acetate was in the middle of this range at 168 mg Co/kg bw. This work indicates that toxicity is related to the cobalt ion and independent of counter ions. Similar results would be expected for the three cobalt carboxylates chemicals in this category.

[1] PBS = phosphate buffered solution without $CaCl_2$ or $MgCl_2$

Table 2. A comparison of acute oral toxicity values of cobalt compounds calculated based on the weight of each compound or on the cobalt content of each respective compound.

Compound	LD50* (mg compound /kg bw)**	LD50* (mg Co/kg bw)
Cobalt(II) fluoride	150	91
Cobalt(II) oxide	202	159
Cobalt(II) phosphate	387	187
Cobalt(II) bromide	406	109
Cobalt(II) chloride	418	190
Cobalt(II) sulphate	424	161
Cobalt(II) nitrate	434	140
Cobalt(II) acetate	503	168

* Data from Speijers et al. (1982)
** Several test compounds were hydrates and contained water. Results are expressed based on the weight of the anhydrous compound.

This toxicity data is supported by evaluation of the absorption, distribution, and elimination of cobalt following exposure to different metal salts. Work by Firriolo et al. (1999) showed that regardless of whether the compound was introduced as Co(II) chloride or Co naphthenate, the absorption, disposition, and elimination of cobalt was the same. These data indicate that the carboxylic acid portion of the salt does not play a role in cobalt ion absorption *in vivo* once the compound (ion pair) has dissociated. These authors state that absorption of cobalt in the GI tract is dependent upon release of free metal ion and their results indicate that the acid, in this case naphthenate, does not limit the degree of absorption.

Firriolo et al. (1999) confirmed previous findings that cobalt absorption occurs in the jejunum of the small intestine. Working with intestinal rings, these authors showed that absorption of cobalt occurred via biochemical processes that occurred at the intestinal mucosal wall. These processes appear to be saturable and both concentration and temperature dependent (Firriolo, 1992). These characteristics are indicative of active transport (Ashmead et al., 1985 and Firriolo et al., 1999). In addition, there appears to be a diffusional component to the absorption of cobalt ions, which is also concentration dependent (Firriolo et al., 1999). Despite the presence of these mechanisms for cobalt absorption, uptake from the gut is incomplete. Only limited absorption of ingested cobalt occurs (e.g., 20% – 30%) in the gut (Firriolo, 1992; ASTDR, 2001).

The *in vivo* toxicity (Speijers et al., 1982) and absorption/distribution data (Firriolo et al. 1999) are supported by the *in vitro* data for a broader range of cobalt carboxylates (Stopford et al., 2003; Firriolo, 1992; Firriolo et al., 1999). This body of work shows that the hazard of these metal carboxylates is largely dependent on the metal, and not the carboxylic acid. This facilitates the use of toxicity data for soluble metal salts (e.g., $Co(II)Cl_2$) that dissociate rapidly and completely under

physiological conditions, to estimate the potential hazard of hexanoic acid, 2-ethyl, cobalt salt; neodecanoic acid, cobalt salt; and fatty acids, C9-C13 neo, cobalt salts.

Supporting Data for Dissociation Products

Consistent with discussions between the Metal Carboxylates Coalition and the EPA, data for the dissociation products (metals and acids) are recognized as being essential to understanding the environmental fate and toxicological characteristics of the respective metal carboxylate salts. Data for 2-ethylhexanoic acid, neodecanoic acid, fatty acids, C9-13 neo, and cobalt chloride are therefore useful in characterizing the hazard of the three HPV compounds.

In summary, the key points relative to hexanoic acid, 2-ethyl, cobalt salt are:

- Dissociation to 2-ethylhexanoic acid and cobalt (described as cobalt chloride);
- Dissociation constant (pK values) in the circum neutral range;
- Complete or nearly complete dissociation at gastric pH (1.5 to 2.0);
- A moderate amount of dissociation in the environmental pH range (neutral);
- Existing data for the parent molecule or its dissociation products will be sufficient to address specific endpoints.

The key points relative to neodecanoic acid, cobalt salt are:

- Dissociation to neodecanoic acid and cobalt (described as cobalt chloride);
- Dissociation constant (pK values) in the circum neutral range;
- Complete or nearly complete dissociation at gastric pH (1.5 to 2.0);
- A moderate amount of dissociation in the environmental pH range (neutral);
- Existing data for the parent molecule or its dissociation products will be sufficient to address specific endpoints.

The key points relative to fatty acids, C9-C13 neo, cobalt salts are:

- Dissociation to fatty acids, C9-C13 neo and cobalt (described as cobalt chloride);
- Dissociation constant (pK values) in the circum neutral range;
- Complete or nearly complete dissociation at gastric pH (1.5 to 2.0);
- A moderate amount of dissociation in the environmental pH range (neutral);
- Existing data for the parent molecule or its dissociation products will be sufficient to address specific endpoints.

Data for the three chemicals and their dissociation products are provided as follows:

Data for hexanoic acid, 2-ethyl, cobalt salt are provided in robust summary format in Appendix A. Appendix B is the IUCLID dataset for 2-ethylhexanoic acid.

Appendix C contains data for neodecanoic acid, cobalt salt in robust summary format. Robust summaries for neodecanoic acid are provided in Appendix D. The IUCLID dataset for neodecanoic acid is attached to Appendix D.

Data for fatty acids, C9-C13 neo, cobalt salts are provided in robust summary format in Appendix E. Appendix F consists of the IUCLID dataset for fatty acids, C9-C13 neo as well as robust summaries prepared by ExxonMobil Chemical Company for C5-C28 neoacids. This category includes fatty acids, C9-C13 neo and neodecanoic acid

Appendix G contains robust summaries for cobalt chloride.

2-ethylhexanoic acid

2-ethylhexanoic acid is used in the manufacture of lubricants, detergents, floatation aids, and corrosion inhibitors, as catalysts for solvent extraction, and for dye granulation, and in the production of alkyd resins used for baking enamels (HSDB, 2005).

For both oral and intravenous administration of 2-ethylhexanoic acid, most (64 – 75%) of the dose was excreted in the urine, with fecal excretion ranging from 2 – 12%. After oral administration, peak blood levels were achieved after 15 to 30 minutes. Dermally-applied compound was both absorbed more slowly and excreted more slowly.

The robust summaries for 2-ethylhexanoic acid were made available to the Coalition by the American Chemistry Council Oxo Process Panel, the members of which volunteered to provide the information to the OECD SIDS program. These robust summaries are attached as Appendix B. In addition, these data are summarized and referenced in the appropriate remarks sections for each data element in the robust summaries for hexanoic acid, 2-ethyl, cobalt salt (Appendix A). Data for 2-ethylhexanoic acid are discussed in the next section and summarized in Table 2.

Neodecanoic Acid

Neodecanoic acid is relatively resistant to biotransformation and does not readily form bioactive metabolites (ExxonMobil Chemical Company, 2002). Thus it would be primarily eliminated in the urine as glucuronic acid conjugates or by deakylation (Katz and Guest, 1994).

The robust summaries for neodecanoic acid were largely derived from information in the IUCLID dataset for neodecanoic acid (attached to Appendix D) and in robust summaries prepared by Exxon-Mobil Chemical Company for the Neoacids (C5 – C28) Category, which includes neodecanoic acid (see Appendix F). In addition, these data are summarized and referenced in the appropriate remarks sections for each data element in the robust summaries of neodecanoic acid, cobalt salt (Appendix C). Data for neodecanoic acid are discussed in the next section and summarized in Table 3.

Fatty Acids, C9-C13 neo

Appendix F contains robust summaries for fatty acids, C9-C13 neo, presented as three parts: the IUCLID dataset for fatty acids, C9-C13 neo (Part 1), the Test Plan for the Neoacids C5-C28 Category (Part 2); and robust summaries for the Neoacids C5 – C28 Category. The information in Appendix F Part 2 and Part 3 was prepared by ExxonMobil Chemical Company. In addition, these data are summarized and referenced in the appropriate remarks sections for each data element in the robust summaries of fatty acids, C9-C13 neo, cobalt salts (Appendix E). Data for fatty acids, C9-C13 neo are discussed in the next section and summarized in Table 3.

Cobalt

Cobalt is a naturally-occurring element that has properties similar to those of iron and nickel. It is an essential element, required for good health in animals and humans (ASTDR, 2001). A biochemically important compound containing cobalt is vitamin B_{12} or cyanocobalamin. For most people, food is the largest source of cobalt intake. The average person consumes about 11 micrograms of cobalt per day in their diet (ASTDR, 2001). Part of this cobalt comes from vitamin B_{12}, which is found in meat and dairy products. Cobalt is also found in surface and groundwater. In the U.S., concentrations in water are usually between 1 and 10 μg/L (ppb), although they may be much higher in areas that are rich in cobalt-containing minerals or in areas near mining or smelting operations. In most drinking water, cobalt levels are less than 1 – 2 ppb (ASTDR, 2001).

Soluble forms of cobalt, such as cobalt(II) chloride (or cobaltous chloride), are most likely to be absorbed and cause systemic effects in humans. For this reason, this compound has often been used in absorption and toxicology studies to determine the potential hazard of cobalt exposures. When coming into contact with water and biological fluids, cobaltous chloride dissolves and releases cobalt

as a (+2) ion. In general, it is the cobalt ion that is responsible for causing toxicity[2]. Because of this, in this document, the toxicity of cobalt(II) chloride (expressed in terms of the cobalt ion), is used as a surrogate for the toxicity of cobalt that is released through the dissociation of the three metal carboxylate salts that are the subject of this test plan.

Approximately 13-34% of cobalt(II) chloride is absorbed in the gut of rats. Absorption may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces (the unabsorbed fraction) and secondarily in urine (the absorbed fraction). For cobalt(II) chloride, 70 - 80% of the administered dose is eliminated in the feces. Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR, 2001).

The robust summaries for cobalt chloride were derived largely from well recognized and peer reviewed compendia (e.g., ATSDR Toxicological Profiles, WHO Environmental Health Criteria). These data are presented in Appendix G. In addition, these data are summarized and referenced in the appropriate remarks sections for each data element in the robust summaries of the three metal carboxylate salts. Data for the soluble/dissociable forms of the metal (free metal or the chloride salt) are discussed in the next section and summarized in Table 3.

EXISTING DATA FOR METAL CARBOXYLATE SALTS AND DISSOCIATION PRODUCTS - SUMMARY

Physicochemical Properties

Available physicochemical property data for hexanoic acid, 2-ethyl, cobalt salt, neodecanoic acid, cobalt salt, and fatty acids, C9-C13 neo, cobalt salts, as well as for their dissociation products, are shown in Table 3 and briefly summarized below. The sources of information for these data are given in the robust summaries (Appendixes A – G).

Recent studies were conducted to determine the melting point, boiling point, and water solubility for the three metal carboxylate salts. Data for these endpoints are also available for all of the dissociation products (Table 3).

[2] Insoluble compounds that do not release significant amounts of the cobalt ion are much less toxic when administered orally (ASTDR, 2001). The oral toxicity of soluble cobalt compounds is similar when expressed in terms of the cobalt ion.

Melting Point

Hexanoic acid, 2-ethylhexyl, cobalt salt

A GLP study was conducted according to OECD Guideline 102, using thermal analysis with a calorimeter, to determine the melting point/melting range of hexanoic acid, 2-ethyl, cobalt salt. The results indicated that the test substance probably melted under decomposition at 120ºC. The melting point for 2-ethylhexanoic acid was reported as -118.4ºC and for cobalt chloride, as 735ºC.

Neodecanoic acid, cobalt salt

A GLP study was conducted according to OECD Guideline 102, using a combination of thermal analysis with a calorimeter and visual testing with the capillary method, to determine the melting point/melting range of neodecanoic acid, cobalt salt. The result (reported as the freezing point) was -27ºC to -26ºC. For neodecanoic acid, the melting point was reported as -39°C; and for cobalt chloride, 735ºC.

Fatty acids, C9-C13 neo, cobalt salts

A GLP study was conducted according to OECD Guideline 102, using thermal analysis with a calorimeter, to determine the melting point/melting range of fatty acids, C9-C13 neo, cobalt salts. The test substance did not melt under the conditions of the test. The melting point for fatty acids, C9-C13 neo was reported as less than -20ºC, and for cobalt chloride, 735ºC.

Boiling Point

Hexanoic acid, 2-ethylhexyl, cobalt salt

A GLP study was conducted according to OECD Guideline 103, using the visual test with capillary tester, to determine the boiling point/boiling range of hexanoic acid, 2-ethyl, cobalt salt. Decomposition occurred at about 120ºC and the boiling point could not be determined. For 2-ethylhexanoic acid, the boiling point was reported as 227.6ºC, and for cobalt chloride, as 1,049ºC.

Neodecanoic acid, cobalt salt

The reported boiling point for neodecanoic acid, cobalt salt was 426 - 517ºC. For neodecanoic acid, the boiling point was reported as 243 - 253ºC, and for cobalt chloride, 1,049ºC.

Fatty acids, C9-C13 neo, cobalt salts

A GLP study was conducted according to OECD Guideline 103, using both thermal analysis with a calorimeter and visual testing with capillary tester, to determine the boiling point/boiling range of fatty acids, C9-C13 neo, cobalt salts. A boiling point or boiling range could not be determined under conditions of the test. For fatty acids, C9-C13 neo, the boiling range was reported as 195 - 280ºC, and for cobalt chloride, the reported boiling point was 1,049ºC.

Density

Hexanoic acid, 2-ethyl, cobalt salt
No information is available on the density of hexanoic acid, 2-ethyl, cobalt salt. The reported density for 2-ethylhexanoic acid is 0.903 and the reported density for cobalt chloride is 3.367 g/cm^3 at 25ºC.

Neodecanoic acid, cobalt salt
The reported density for neodecanoic acid, cobalt salt is 1.07 at 25ºC. For neodecanoic acid, the density is 0.91 at 20ºC, and for cobalt chloride, 3.367 at 25ºC.

Fatty acids, C9-C13 neo, cobalt salts
The reported density for fatty acids, C9-C13 neo, cobalt salts is 1.14 at 25ºC. For fatty acids, C9-C13 neo, the density is 0.923 at 20º, and for cobalt chloride, 3.367 at 25ºC.

Vapor Pressure

Hexanoic acid, 2-ethyl, cobalt salt
Information on vapor pressure was not available for hexanoic acid, 2-ethyl, cobalt salt. The reported vapor pressure for 2-ethylhexanoic acid was 1.33 x 10^{-3} kPa at 20ºC. Vapor pressure was not considered applicable for cobalt chloride.

Neodecanoic acid, cobalt salt
Information on vapor pressure was not available for neodecanoic acid, cobalt salt. The reported vapor pressure for neodecanoic acid was 0.29 hPa at 50°C. Vapor pressure was not considered applicable for cobalt chloride.

Fatty acids, C9-C13 neo, cobalt salts
Information on vapor pressure was not available for fatty acids, C9-C13 neo, cobalt salts. The reported vapor pressure for fatty acids, C9-C13 neo was 0.0065 hPa at 22.1ºC. Vapor pressure was not considered applicable for cobalt chloride.

Partition Coefficient

The octanol/water partition coefficient is not relevant for ionizeable substances such as the metal carboxylate salts, nor is it relevant for inorganic chemicals such as cobalt chloride. However, this endpoint is relevant and is available for each of the acid dissociation products. For 2-ethylhexanoic acid, the log Kow was calculated to be 3.0. For neodecanoic acid, the log Kow was calculated to be 3.90. The log Kow for fatty acids, C9-C13 neo was determined experimentally to be 3.05 – 3.17.

Water Solubility

Hexanoic acid, 2-ethyl, cobalt salt
A GLP study was conducted, following OECD Guideline 105, using the column elution method, to determine the water solubility of hexanoic acid, 2-ethyl, cobalt salt. The water solubility was determined to be 28.8 mg/L at 20ºC. The water solubility of 2-ethylhexanoic acid is similar, reported to be 25 mg/L at 25ºC. Cobalt chloride is an order of magnitude more soluble in water, with a reported value of 450 g/L at 7ºC.

Neodecanoic acid, cobalt salt
A GLP study was conducted, following OECD Guideline 105, using the column elution method, to determine the water solubility of neodecanoic acid, cobalt salt. The water solubility was determined to be 309.5 mg/L at 20ºC. The water solubility of neodecanoic acid was reported to be 68.97 mg/L at 25ºC. For cobalt chloride, the reported value was 450 g/L at 7°C.

Fatty acids, C9-C13 neo, cobalt salts
A GLP study was conducted, following OECD Guideline 105, using the column elution method, to determine the water solubility of fatty acids, C9-C13 neo, cobalt salts. The water solubility was determined to be 28.3 mg/L at 20ºC. For fatty acids, C9-C13 neo, the reported water solubility was 490 mg/L at a pH of 3 and 3800 mg/L at a pH of 7 (both at 20ºC). The water solubility of cobalt chloride is reported as 450 g/L at 7°C.

Environmental Fate and Transport

Available environmental fate and transport data for hexanoic acid, 2-ethyl, cobalt salt, neodecanoic acid, cobalt salt, and fatty acids, C9-C13 neo, cobalt salts, and for their dissociation products, are shown in Table 3 and briefly summarized below. The sources of information for these data are given in the robust summaries (Appendixes A – G).

Data exist for dissociation in water for all three metal carboxylate salts, but not for any other fate characteristics. With the exception of the dissociation data, the relevant information discussed below pertains to the respective acids and cobalt.

Photolysis

The predicted photolytic half-lives for 2-ethylhexanoic acid and neodecanoic acid are 16 hours and 17 hours, respectively, according to AOP v.1.91 in the EPIWIN v.311 program. A prediction for fatty acids, C9-C13 neo was not available in EPIWIN. The photodegradability of cobalt chloride is not relevant, as the element cobalt does not degrade further.

Dissociation in water

One key characteristic of any metal carboxylate is that it readily dissociates from an ion pair into free metal and free acid as the pH is decreased. Dissociation studies were conducted to determine the equilibrium constant for each of the three metal carboxylate salts.

Hexanoic acid, 2-ethyl, cobalt salt
A dissociation study was conducted according to OECD 112, under GLPs, to determine the equilibrium constant of hexanoic acid, 2-ethyl, cobalt salt. The resulting pKa was 6.41 at 20ºC.

Neodecanoic acid, cobalt salt
A dissociation study was conducted according to OECD 112, under GLPs, to determine the equilibrium constant of neodecanoic acid, cobalt salt. The resulting pKa was 6.52 at 20ºC.

Fatty acids, C9-C13 neo, cobalt salts
A dissociation study was conducted according to OECD 112, under GLPs, to determine the equilibrium constant of fatty acids, C9-C13 neo, cobalt salts. The resulting pKa was 5.96 at 20ºC.

Biodegradation

No data are available on biodegradation of any of the three metal carboxylate salts. For 2-ethylhexanoic acid, an aerobic biodegradation study similar to OECD 301D indicated a BOD_{20} of 83% of theoretical. According to the manometric respirometry test (OECD 301F), neodecanoic acid is not readily biodegradable, with only 11% degradation after 28 days. Fatty acids, C9-C13 neo were not readily biodegradable, with approximately 2% degraded over 28 days in two different studies (per OECD 301F and Directive 84/449/EEC, C.4). Biodegradation is not relevant for the element cobalt.

Monitoring data

No monitoring data were reported.

Transport data

Estimation of environmental transport for the three metal carboxylate salts is not available since fate models generally used do not accurately predict salts such as metal carboxylates. However, the distribution of two of the component acids was predicted using the Level III Fugacity model in EPIWIN v.3.11, assuming equal input to all compartments. For 2-ethylhexanoic acid, the distribution was predicted as 5.29% in air, 41.6% in water, 53% in soil, and 0.197% in sediment. For neodecanoic acid, the distribution was predicted as 3.55% in air, 37% in water, 57.5% in soil and 1.96% in sediment. A similar prediction for fatty acids, C9-C13 neo was not available in EPIWIN.

Ecotoxicity

There are no available ecotoxicity data for the three metal carboxylate salts. (Although studies were conducted with hexanoic acid, 2-ethyl, cobalt salt, they are not considered reliable). Available date for the dissociation products are shown in Table 3 and briefly summarized below. The sources of information for these data are given in the robust summaries (Appendixes A – G).

Fish Toxicity

There are no data on the toxicity of the three metal carboxylate salts to fish; however, the dissociation products are reported to be moderately toxic to fish.

2-ethylhexanoic acid
In a static acute test with fathead minnows (*Pimephales promelas*), the 96-h LC50 was reported to be 70 mg/Lat a pH of 5.3 – 5.5 (test solutions were not buffered).

Neodecanoic acid
Static acute renewal tests of water-accommodated fractions of neodecanoic acid indicated a 96-h LC50 for rainbow trout (*Oncorhynchus mykiss*) of 37.2 mg/L; other reported values range from 32 – 181 mg/L.

Fatty acids, C9-C13 neo
In a semi-static test using water-accommodated fractions, the reported 96-h LC50 of fatty acids, C9-C13 neo for the rainbow trout (*Oncorhynchus mykiss*) was 46 mg/L.

Cobalt chloride
For cobalt chloride, the 96-h LC50 was 1.41 mg Co/L for the highly sensitive rainbow trout, *Oncorhynchus mykiss*. Other fish species were less sensitive with 96-h LC50 values ranging from 22.0 to 330 mg Co/L.

Invertebrate toxicity

There are no data on the toxicity of the three metal carboxylate salts to invertebrate species; however, the dissociation products are reported to be moderately toxic to invertebrates.

2-ethylhexanoic acid
The reported 48-h EC50 for *Daphnia magna* for 2-ethylhexanoic acid was 85.4 mg/L.

Neodecanoic acid
For neodecanoic acid, the 48-h LL50 (lethal limit for 50%) to *Daphnia magna* was reported as 47.1 mg/L, while the 96-h LC50 for the copepod *Acartia tonsa* was 25 mg/L.

Fatty acids, C9-C13 neo

Using water-accommodated fractions, the reported 48-h EC50 of fatty acids, C9-C13 neo for *Daphnia magna* was 41 mg/L.

Cobalt chloride

For cobalt chloride, reported 48-h EC50 values for *Daphnia magna* include 1.52 mg Co/L and 5.5 mg Co/L. For *Ceriodaphnia dubia*, 48-h LC50 values ranged from 2.35 to 4.60 mg Co/L.

Algal toxicity

There are no data on the toxicity of the three metal carboxylate salts to algae. Available data for the dissociation products are discussed below.

2-ethylhexanoic acid

For 2-ethylhexanoic acid, the 96-h EC50 for *Scenedesmus subspicatus* was 40.6 mg /L based upon biomass and 44.4 mg/L based upon growth rate.

Fatty acids, C9-C13 neo

Using water-accommodated fractions of fatty acids, C9-C13 neo, the 72-h EC50 for *Selenastrum capricornutum* was 55 – 160 mg/L, based upon growth rate. However, the pH was not adjusted so the effects are thought to be due to pH rather than the test substance. When the pH was adjusted, the EC50 was greater than 1000 mg/L.

Cobalt chloride

For cobalt chloride, the 96-h EC50 for *Chlorella vulgaris* was 0.52 mg Co/L. For the duckweed *Lemna minor*, the 7-d IC50 was 16.9 mg Co/L, while for the blue-green alga *Spirulina platensis*, the 96-h EC50 was 23.8 mg Co/L.

In summary, there are no reliable ecotoxicity data on the three metal carboxylate salts. 2-ethylhexanoic acid is moderately toxic to fish, invertebrates and algae. Neodecanoic acid is moderately toxic to fish and invertebrates; toxicity to algae is unknown. Fatty acids, C9-C13 neo are moderately toxic to fish and invertebrates; toxicity to algae appears to be related to pH effects. Cobalt chloride is of moderate toxicity to fish and invertebrates, but appears to be highly toxic to at least some species of aquatic plants

Human Health Effects

Data exist for a number of human health effects endpoints for hexanoic acid, 2-ethyl, cobalt salt. There are no data available for any of these endpoints for neodecanoic acid, cobalt salt or for fatty acids, C9-C13 neo, cobalt salts. However, the majority of the human health effects endpoints are satisfied for the dissociation products: 2-ethylhexanoic acid, neodecanoic acid, fatty acids, C9-C13 neo, and cobalt chloride. These data are shown in Table 3 and briefly summarized below. The sources of information for these data are given in the robust summaries (Appendixes A – G).

Acute Mammalian Toxicity

Hexanoic acid, 2-ethyl, cobalt salt

Acute toxicity data are available for hexanoic acid, 2-ethyl, cobalt salt for three of five acute endpoints (i.e., oral toxicity, inhalation toxicity, and dermal toxicity), as presented in Table 3. The acute oral LD50 for the rat was 1220 mg/kg for females and 1550 mg/kg for males. The inhalation LC50 for a 1-hour exposure of rats was > 10 mg/L (the maximum attainable nominal concentration). The dermal LD50 was > 5000 mg/kg for rabbits. Skin and eye irritation studies were not available.

2-ethylhexanoic acid

Acute toxicity data are available for 2-ethylhexanoic acid for five of five acute endpoints (i.e., oral toxicity, inhalation toxicity, dermal toxicity, skin irritation and eye irritation), as presented in Table 3. In general, the data indicate a low order of acute toxicity. The acute oral LD50 for the rat was between 1600 and 3200 mg/kg. The inhalation LC50 for a 6-hour exposure of rats was > 2.36 mg/L. In an acute dermal toxicity study with guinea pigs, the LD50 was < 5.0 mL/kg. Slight irritation to the skin was observed after 4 hours exposure in rabbits, while severe corneal irritation was observed in the eyes of rabbits after 24 hours.

Neodecanoic acid

Acute toxicity data are available for neodecanoic acid for five of five acute endpoints (i.e., oral toxicity, inhalation toxicity, dermal toxicity, skin irritation and eye irritation), as presented in Table 3. Neodecanoic acid shows a low order of acute toxicity. Oral, inhalation and dermal LD50 or LC50 values are 2000 mg/kg (rat), >511 mg/m^3 (6 hrs., rat), and >3160 mg/kg (rabbit) or >3640 mg/kg (rat), respectively. Neodecanoic acid was non-irritating to the skin when tested on the rabbit according to OECD Guideline 404, but did cause eye irritation in the rabbit using the Draize test.

Fatty acids, C9-C13 neo

Acute toxicity data are available for fatty acids, C9-C13 neo for four out of five acute toxicity endpoints (all except inhalation), as presented in Table 3, and indicate a low order of toxicity. For rats, the acute oral LD50 was 2859 mg/kg

and the acute dermal LD50 was > 2000 mg/kg. No inhalation studies were available. Fatty acids, C9-C13 neo were not irritating to the skin or eyes of rabbits.

Cobalt chloride

There are extensive toxicity data available for cobalt (II) chloride and several other soluble and insoluble salts of cobalt. The single-dose rat LD50s for cobalt (II) chloride range from 19.8 to 190 mg Co/kg bw. For the mouse, the LD50 value expressed as the cobalt ion is 89.3 mg Co/kg bw. Dermatitis, probably caused by an allergic reaction, is a common result of dermal exposure to cobalt in humans.

Repeated Dose Toxicity

2-ethylhexanoic acid

A number of repeated dose toxicity studies have been conducted with 2-ethylhexanoic acid. In the preferred study, rats were fed diets containing 2-ethylhexanoic acid for 13 weeks and allowed 28 days of recovery. All toxicity was reversible within 28 days. No mortality or treatment-related signs of toxicity occurred at any of the three dose levels. Body weight changes, hematology, blood chemistry, and organ weight differences were noted, except in the lowest dose group. The NOAEL was approximately 300 mg/kg/day, and the NOEL was approximately 65 mg/kg/day. The results are consistent with four other repeated dose studies in rats. In a similar 13-week dietary exposure study with mice, the NOAEL was approximately 200 mg/kg/day.

Neodecanoic acid

Repeated dose studies have been conducted on neodecanoic acid for several species and several exposure routes. When administered to rats in their feed for 3 months, the NOAEL for a 30% preparation of neodecanoic acid was 500 ppm. The LOAEL was 1500 ppm and included changes in the renal tubules of both male and female rats. Morphological changes in the thyroid, including hyperplasia, were also seen in male rats at the 1500 ppm level. Beagle dogs receiving oral capsules containing neodecanoic acid daily for a period of 13 weeks did not show adverse effects at 30 mg/kg and below, while effects on body weight, hematocrit, hemoglobin and erythrocytes were seen at doses of 94.8 mg/kg and higher. Albino rabbits receiving 10 dermal applications of neodecanoic acid over a 14-day period showed no systemic effects, resulting in a NOAEL of 2.26 g/kg.

Fatty acids, C9-C13 neo
Administration by daily gavage over 4 weeks to rats resulted in a NOAEL of 300 mg/kg (the highest dose); the LOAEL was therefore greater than 300 mg/kg. No adverse toxic effects were observed in any of the female treatment groups; effects observed in the kidneys of the males were specific to young male rats and not of toxicological significance to humans.

Cobalt chloride
Oral dosing of rats with cobalt chloride five days per week for 150 to 210 days indicated a LOAEL of 4 mg Co/kg based upon increased organ weights. This is consistent with other studies of cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg-day. Repeated oral dosing of rats with cobalt chloride hexahydrate for 8 weeks indicated the NOAEL was 0.6 mg Co/kg and the LOAEL was 2.5 mg Co/kg, based upon changes in hemoglobin content and numbers of erythrocytes. Another study reported oral doses of 0.5 and 2.5 mg Co/kg for 7 months stimulated hematopoiesis and decreased immunological reactivity in rats, while doses of 0.05 mg Co/kg had no effects.

Genetic Toxicity – in vitro

The *in-vitro* genetic toxicity endpoint is fulfilled for hexanoic acid, 2-ethyl, cobalt salt as well as for all of the dissociation products in this category.

Hexanoic acid, 2-ethyl, cobalt salt
Hexanoic acid, 2-ethyl, cobalt salt produced negative results in the Ames assay with five strains of *Salmonella typhimurium* (e.g., TA 98, TA100, TA1535, TA1537, and TA1538) when tested with and without metabolic activation. Results were also negative for the bacterial DNA damage or repair assay with *E. coli*, tested with and without activation.

2-ethylhexanoic acid
In the Ames assay, 2-ethylhexanoic acid produced negative results with four strains of *S. typhimurium* (TA97, TA98, TA100, and TA1535), tested with and without metabolic activation.

Neodecanoic acid
Neodecanoic acid produced negative results in the Ames *Salmonella* assay (OECD Method 471) against four strains of bacteria (e.g., TA 98, TA100, TA1535, and TA1537) when tested with and without metabolic activation. Neodecanoic acid also produced negative results in a cytogenetic assay (OECD Method 473) with cultured human lymphocytes when tested both with and without metabolic activation.

Fatty acids, C9-C13, neo
Fatty acids, C9-C13, neo acid produced negative results in the bacterial gene mutation assay against four strains of *S. typhimurium* and one strain of *E. coli* when tested both with and without metabolic activation. When tested in a

cytogenetic assay with Chinese hamster ovary cells, results were negative in the absence of metabolic activation but positive in the presence of S9.

Cobalt chloride

Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt chloride, are generally non-mutagenic in bacterial assays, including plate incorporation and fluctuation assays with *Salmonella typhimurium* TA strains and *Escherichia coli* WP2. However, a weak positive mutagenic response has been found in the rec-assay with *Bacillus subtilis* and in Chinese hamster V9 cells. DNA damage in isolated human lymphocytes was observed at 6.0 mg Co/L in the alkaline comet assay, and an increase in sister chromatid exchanges has been observed in human lymphocytes and macrophages.

Genetic Toxicity – in vivo

The *in vivo* genetic toxicity endpoint is fulfilled for hexanoic acid, 2-ethyl, cobalt salt, 2-ethylhexanoic acid, and cobalt chloride.

Hexanoic acid, 2-ethyl, cobalt salt

No evidence of mutagenic potential was found for hexanoic acid, 2-ethyl, cobalt salt in the mouse micronucleus mutagenicity assay. In this study, mice were given three dose levels (by gavage in corn oil, two times) of the test material (total dose up to 5000 mg/kg). Treated groups produced similar micronucleated cell counts as in the control and there was no effect upon the ratio of monochromatic to polychromatic erythrocytes.

2-ethylhexanoic acid

2-ethylhexanol was tested in the mouse micronucleus assay. This study is relevant to 2-ethylhexanoic acid since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid. In the study, no increased incidences of micronuclei in polychromatic erythrocytes was observed in mice receiving the test substance (456 mg/kg of 2-ethylhexanol in corn oil) via intraperitoneal injection.

Cobalt chloride

Oral administration of cobalt chloride hexahydrate to mice (20 – 80 mg/kg bw) produced a concentration-dependent increase in chromosomal aberrations. A dose-dependent increase in the incidence of micronucleated polychromatic erthythrocytes was observed in mice subsequent to i.p. injection of $CoCl_2.6H_20$, at doses of 25 – 90 mg Co/kg bw. Increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (NOEL).

In summary, hexanoic acid, 2-ethyl, cobalt salt, 2-ethylhexanoic acid, neodecanoic acid, and fatty acids, C9-C13 neo are not genotoxic in the majority of studies reported. Cobalt chloride has demonstrated positive effects in various *in vitro* or *in vivo* studies.

Developmental Studies

No developmental studies with the three metal carboxylate salts are available. However, data exist for the dissociation products 2-ethylhexanoic acid, neodecanoic acid, and cobalt chloride.

2-ethylhexanoic acid

Several teratogenicity/developmental studies have been conducted with 2-ethylhexanoic acid (Appendix B). The preferred studies were conducted with rats and rabbits. Rats were treated by gavage on days 6 through 15 of gestation. For rats, the NOEL for teratogenic and developmental effects was 100 mg/kg/day, reflecting effects upon fetal body weight and reduced ossification. There was no evidence of teratogenicity. The NOEL for maternal effects in rats was 250 mg/kg/day. Rabbits were treated by gavage on days 6 through 18 of gestation. No fetal or embryo-toxicity was noted, and the NOEL for offspring was equal to the highest dose (250 mg/kg). The NOEL for maternal effects in rabbits was 25 mg/kg/day.

Neodecanoic acid

Information on developmental toxicity is available from a 3-generation study with rats that received neodecanoic acid in their diet (Appendix F, Part 3). The pups (F1 and F2 generation) born to parents fed up to 1500 ppm neodecanoic acid did not show any effects upon body weight, appearance or behavior, and there were no treatment-related findings of toxicity, abnormality, or pathology.

Cobalt chloride

In a developmental toxicity study with cobalt chloride exposure (5.4 to 21.8 mg Co/kg/day) in rats from gestation day 14 to lactation day 21, the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects were observed on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12.

Reproduction Studies

No reproduction studies with the three metal carboxylate salts are available. However, data exist for the dissociation products 2-ethylhexanoic acid, neodecanoic acid, and cobalt chloride.

2-ethylhexanoic acid

A one-generation reproduction study was conducted with 2-ethylhexanoic acid (as sodium 2-ethylhexanoate). Male and female rats were treated with 0, 100, 300, or 600 mg/kg of the test substance in drinking water. Effects on maternal

animals were noted at the highest dose, resulting in a NOEL of 300 mg/kg. The NOEL for the F1 generation was reported as 100 mg/kg.

Neodecanoic acid
In an oral (feeding) multi-generation rat reproduction study with neodecanoic acid, no adverse effects were observed in the parental generation or the F_1 and F_2 generations at feeding levels up to 1500 ppm in the diet.

Cobalt chloride
Cobalt exposure (as cobalt chloride hexahydrate in drinking water for 12 -13 weeks) affected male reproductive parameters for mice in a time- and dose-dependent manner. All dose levels (23.0 – 72.1 mg Co/kg-day) caused decreases in testicular weight and epididymal sperm concentration. Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water.

Other Information

Neodecanoic acid
Neodecanoic acid was not found to be a skin sensitizer when tested on the guinea pig.

Fatty acids, C9-C13 neo
Fatty acids, C9-C13 neo was not found to be sensitizing when testing on the guinea pig.

Cobalt chloride
The U.S. National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals. "No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt." (ATSDR Sept 2001 Draft).

Table 3. Summary of existing data for hexanoic acid, 2-ethyl, cobalt salt; neodecanoic acid, cobalt salt; fatty acids, C9-C13 neo, cobalt salts; and their dissociation products[1]

SIDS ENDPOINT	REPORTED VALUES						
	Hexanoic acid, 2-ethyl, cobalt salt	2-ethylhexanoic acid	Neodecanoic acid, cobalt salt	Neodecanoic acid	Fatty acids, C9-C13 neo, cobalt salts	Fatty acids, C9-C13 neo	Cobalt chloride
Physicochemical Properties							
Melting Point	Approx. 120ºC	-118.4ºC	-26 to -27ºC	-39ºC	Could not be determined	< -20ºC	735ºC
Boiling Point	Could not be determined	227.6ºC	426 - 517ºC	243-253ºC	Could not be determined	195 - 280ºC	1,049ºC
Density	--	0.903	1.07 at 25ºC	0.91 at 20ºC	1.14 at 25ºC	0.923 at 20ºC	3.367 at 25ºC
Vapor pressure	NR	1.33×10^{-3} kPa at 20ºC	NR	0.29 hPa at 50ºC	NR	0.0065 hPa at 22.1ºC	NR
Log Partition Coefficient	NR	3.0	NR	3.90	NR	3.05 – 3.17	NR
Water Solubility	28.8 mg/L at 20ºC	25 mg/L at 25º	309.5 mg/L at 20ºC	68.97 mg/L at 25ºC	28.3 mg/L at 20ºC	490 mg/L at pH=3, 3800 mg/L at pH =7; 20ºC	450 g/L at 7ºC
Environmental Fate							
Photodegradation	--	Half-life of 16 hours for indirect photolysis	--	Half life of 17 h for indirect photolysis	--	--	NR
Dissociation in water	pKa = 6.41at 20ºC	--	pKa = 6.52 at 20ºC	--	pKa = 5.96 at 20ºC	--	--
Monitoring Data	--	--	--	--	--	--	--
Transport (Fugacity)	--	5.29% in air, 41.6% in water, 53% in soil, 0.197% in sediment	--	3.55% in air, 37% in water, 57.5% in soil, 1.96% in sediment	--	--	NR
Biodegradation	--	BOD_{20} at 83% of theoretical	--	11% degradation after 28 days	--	Approx. 2% degradation after 28 days	NR
Ecotoxicity							
Fish toxicity (96-h)	Reliable information not available	70 mg/L (fathead minnow)	--	37.2 mg/L (rainbow trout)	--	46 mg/L (rainbow trout)	1.41 - 333 mg/L; rainbow trout most sensitive
Invertebrate toxicity (48-h)	Reliable information not available	85.4 mg/L (*Daphnia magna*)	--	47.1 mg/L (*Daphnia magna*, LL50)	--	41 mg/L (*Daphnia magna*)	1.52 – 5.5 mg Co/L (Daphnia magna)
Algae toxicity	Reliable information not available	40.6 – 44.4 mg/L (*Scenedesmus subspicatus*)	--	--	--	55 – 160 mg/L (*Selenastrum capricornutum*, 72-h EC50)	0.52 mg Co/L (*Chlorella vulgaris*, 96-h EC50)

SIDS ENDPOINT	REPORTED VALUES						
	Hexanoic acid, 2-ethyl, cobalt salt	2-ethylhexanoic acid	Neodecanoic acid, cobalt salt	Neodecanoic acid	Fatty acids, C9-C13 neo, cobalt salts	Fatty acids, C9-C13 neo	Cobalt chloride
Human Health Effects							
Acute Oral LD50	1220 – 1550 mg/kg (rat)	1600 – 3200 mg/kg (rat)	--	2000 mg/kg (rat)	--	2859 mg/kg (rat)	19.8 – 190 mg Co/kg (rat); 89.3 mg Co/kg (mouse)
Inhalation LC50	>10 mg/L (rat, 1-h exposure)	> 2.36 mg/L (rat; 6 hr exposure)	--	>511 mg/m^3 (rat, 6-h exposure)	--	--	--
Dermal LD50	>5000 mg/kg (rabbit)	<5.0 mL/kg (guinea pig)	--	>3160 mg/kg (rabbit); >3640 mg/kg (rat)	--	> 2000 mg/kg (rat)	Increased proliferation of lymphatic cells at 9.6 – 14.7 mg Co/kg-day (various spp.)
Skin irritation	--	Slight irritation in rabbits after 4 hrs.	--	Non-irritating (rabbit)	--	Not irritating (rabbit)	Allergic dermatitis seen in humans
Eye irritation	--	Severe corneal irritation in rabbits after 24 hrs.	--	Irritating (rabbit)	--	Not irritating (rabbit)	--
Repeated dose	--	For 13-week dietary exposure, NOAEL ~300 mg/kg/day for rats and ~200 mg/kg/day for mice	--	500 ppm NOAEL for 3 month oral exposure of rats; 30 mg/kg NOAEL for 13 week oral exposure in dogs; 2.26 g/kg NOAEL for 14 day dermal exposure of rabbits	--	NOAEL = 300 mg/kg; LOAEL = >300 mg/kg based on 4 week exposure of rats via gavage	4 mg Co/kg LOAEL for rats (organ weight changes); 0.6 mg Co/kg NOAEL for rats (blood parameter changes); LOAELs 0.5 – 30.2 mg Co/kg-day for rats in various studies
Genetic toxicity (*in vitro*)	Negative in Ames assay with *Salmonella* and in bacterial DNA damage or repair assay with *E. coli*	Negative in Ames assay with *Salmonella*	--	Negative for *Salmonella*, human lymphocytes	--	Negative for *S. typhimurium* and *E. coli*. Negative for Chinese hamster ovary cells without activation but positive in the presence of S9	Co(2+) generally non-mutagenic in most bacterial assays; weak positive response with Chinese hamster V9 cells; DNA damage in human lymphocytes

SIDS ENDPOINT	REPORTED VALUES						
	Hexanoic acid, 2-ethyl, cobalt salt	2-ethylhexanoic acid	Neodecanoic acid, cobalt salt	Neodecanoic acid	Fatty acids, C9-C13 neo, cobalt salts	Fatty acids, C9-C13 neo	Cobalt chloride
Genetic toxicity (*in vivo*)	Negative in mouse micronucleus test	Negative in mouse micronucleus test	--	--	--	--	Clastogenic effects in mice
Developmental	--	No evidence of teratogenicity. In rats, NOEL = 100 mg/kg/day for offspring, 250 mg/kg/day for maternal animals. For rabbits, NOEL = 250 mg/kg/day for offspring, 25 mg/kg/day for maternal animals.	--	No effects in F_1 or F_2 pups from parents fed up to 1500 ppm in diet	--	--	NOAEL = 24.8 mg/kg/day in rats; 81.7 mg Co/kg in screening study (mice)
Reproductive	--	NOEL for P generation = 300 mg/kg; NOEL for F_1 generation = 100 mg/kg	--	No effects in parental, F_1 or F_2 generations of rats at dietary levels up to 1500 ppm	--	--	Effects in rats at 13.2 – 30.2 mg Co/kg/day; in mice at 23 – 58.9 mg Co/kg/day

[1] References are given in the robust summaries (Appendixes A – G)
[2] NR = not relevant

TEST PLAN AND RATIONALE

Hexanoic acid, 2-ethyl, cobalt salt	CASRN 136-52-7
Neodecanoic acid, cobalt salt	CASRN 27253-31-2
Fatty acids, C9-C13 neo, cobalt salts	CASRN 68955-83-9

The Test Plan for the three metal carboxylate salts in this category is presented in Table 4 with supporting data for the dissociation products. The rationale for the Test Plan is based upon existing data as summarized in the previous section and in Table 3. The majority of the recommended testing is proposed for neodecanoic acid, cobalt salt. This compound is of intermediate chain length (C10) relative to the other two metal carboxylates salts (C8 for hexanoic acid, 2-ethyl, cobalt salt and C9-C13 for fatty acids, C9-C13 neo, cobalt salts) and is thus selected as representative of the category. Using the read-across approach, data generated for neodecanoic acid, cobalt salt will be used to fulfill applicable endpoints for the category.

Physicochemical Properties

Almost without exception, data are available for all five SIDS endpoints listed in Tables 3 and 4 for each of the three metal carboxylate salts and their dissociation products. A series of GLP studies were conducted for the Metal Carboxylates Coalition to generate melting point, boiling point and water solubility data for the salts, although in some cases values could not be determined under the conditions of the test. The vapor pressure endpoint is considered not applicable for the salts. The octanol/water partition coefficient is also not appropriate for the salts, as erroneous data would result if these ionizeable substances were used to determine the Kow.

- No additional testing is recommended or proposed for any of the physico-chemical properties.

Environmental Fate Parameters

GLP studies were conducted to determine the dissociation constant for the three metal carboxylate salts. This is a key property, because the fate and effects of these compounds are based upon the dissociation products. Environmental fate endpoints are available or were estimated for the dissociation products. For 2-ethylhexanoic acid, neodecanoic acid, and fatty acids, C9-C13 neo, experimental data are available for the biodegradation endpoint. Although 2-ethylhexanoic acid was biodegradable, the other two acids were not readily biodegradable. The values for the photodegradation and transport endpoints were predicted using EPIWIN for the three acids. Standard models used for estimating transport do not accurately predict salts or ionized substances and were not used for hexanoic

acid, 2-ethyl, cobalt salt, neodecanoic acid, cobalt salt, or fatty acids, C9-C13 neo, cobalt salts. Endpoints such as photodegradation or biodegradation are not relevant for cobalt chloride because this is a simple compound that releases the element cobalt which does not degrade further.

- Testing is recommended to determine the biodegradation of neodecanoic acid, cobalt salt. This compound is proposed as representative of the three carboxylate salts in this category, as it is intermediate in chain length (C10) relative to the other salts which are C8 or C9-C13.

Ecotoxicity

Ecotoxicity studies were performed for hexanoic acid, 2-ethyl, cobalt salt but are not considered reliable. No ecotoxicity data are available for neodecanoic acid, cobalt salt or fatty acids, C9-C13 neo, cobalt salts. Toxicity studies with fish, invertebrates, and algae are available for 2-ethylhexanoic acid, fatty acids, C9-C13 neo, and cobalt chloride. Data for fish and invertebrates, but not algae, are available for neodecanoic acid. The available data indicate that the acids have similar toxicity to aquatic organisms, while cobalt is somewhat more toxic. Acute toxicity tests with fish, *Daphnia*, and algae are recommended for a representative salt from this category.

- Acute toxicity tests with fish, daphnids and algae are proposed for neodecanoic acid, cobalt salt.

Human Health Effects

Acute toxicity studies

Acute toxicity data are available for hexanoic acid, 2-ethyl, cobalt salt but not for the other two salts in this category. However, acute toxicity is well-characterized for the dissociation products for the majority of the five endpoints (oral toxicity, inhalation, dermal toxicity, skin irritation, and eye irritation).

- An acute oral LD50 study with the rat is proposed for neodecanoic acid, cobalt salt.

Genotoxicity studies

Both *in vitro* and *in vivo* genotoxicity studies have been completed with hexanoic acid, 2-ethyl, cobalt salt, but there are no genotoxicity studies on the other two salts. Available data for the acids indicate that 2-ethylhexanoic acid is not genotoxic in bacterial or mammalian systems. Neodecanoic acid has been

shown to be non-mutagenic *in vitro* in bacteria and human lymphocytes. Fatty acids, C9-C13 neo produced negative results with bacterial systems, but both negative and positive results with mammalian cells. The genotoxicity of cobalt chloride has been well-characterized, and indicates some positive responses.

- Two types of genotoxicity studies are proposed for neodecanoic acid, cobalt salt. For the *in vitro* endpoint, the Ames *Salmonella typhimurium* reverse mutation assay is proposed. For the *in vivo* endpoint, the mouse micronucleus test is proposed. In addition, the mouse micronucleus test is proposed for fatty acids, C9-C13 neo, cobalt salts, since there are positive indications of genotoxicity for both of the dissociation products from this compound.

Higher tiered studies

Data from repeated dose studies are not available for the three metal carboxylate salts. However, a number of repeated dose studies have been conducted with 2-ethylhexanoic acid, neodecanoic acid, fatty acids, C9-C13 neo, and cobalt chloride, in a variety of species.

There are no developmental and reproductive toxicity studies available for the three metal carboxylate salts. Data from developmental and reproductive studies exist for two of the three acids: 2-ethylhexanoic acid and neodecanoic acid. Developmental and reproductive toxicity are well-characterized for cobalt chloride.

- A combined repeated dose with repro/developmental screen (OECD 422) is proposed for neodecanoic acid, cobalt salt.

Table 4. Test Plan Matrix: Hexanoic acid, 2-ethyl, cobalt salt; neodecanoic acid, cobalt salt; and fatty acids, C9-C13 neo, cobalt salts

Data elements	Hexanoic acid, 2-ethyl, cobalt salt				2-ethyl-hexanoic acid			Neodecanoic acid, cobalt salt				Neodecanoic acid			Fatty acids, C9-C13 neo, cobalt salts				Fatty acids, C9-C13 neo			Cobalt chloride		
	Information available	GLP study	Acceptable	Testing needed	Information available	GLP study	Acceptable	Information available	GLP study	Acceptable	Testing needed	Information available	GLP study	Acceptable	Information available	GLP study	Acceptable	Testing needed	Information available	GLP study	Acceptable	Information available	GLP study	Acceptable
PHYSICOCHEMICAL PROPERTIES																								
Melting Point	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	U	Y	Y	Y	Y	N	Y	U	Y	Y	N	Y
Boiling Point	Y	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	U	Y	Y	Y	Y	N	Y	U	Y	Y	N	Y
Vapor pressure	NR	-	-	N	Y	N	Y	NR	-	-	N	Y	U	Y	NR	-	-	N	Y	Y	Y	NR	-	-
Partition Coefficient	NR	-	-	N	Y	N	Y	NR	-	-	N	Y	N	Y	NR	-	-	N	Y	Y	Y	NR	-	-
Water Solubility	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	U	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
ENVIRONMENTAL FATE PARAMETERS																								
Photodegradation	N	-	-	N	Y	N	Y	N	-	-	N	Y	N	Y	N	-	-	N	N	-	-	NR	-	-
Dissociation in water	Y	Y	Y	N	NR	-	-	Y	Y	Y	N	NR	-	-	Y	Y	Y	N	NR	-	-	NR	-	-
Transport	N	-	-	N	Y	N	Y	N	-	-	N	Y	N	Y	N	-	-	N	N	-	-	NR	-	-
Biodegradation	N	-	-	RA	Y	N	Y	N	-	-	Y	Y	Y	Y	N	-	-	RA	Y	Y	Y	NR	-	-
ECOTOXICITY																								
Fish toxicity (96-h)	N	-	-	RA	Y	N	Y	N	-	-	Y	Y	Y	Y	N	-	-	RA	Y	Y	Y	Y	N	Y
Invertebrate toxicity (48-h)	N	-	-	RA	Y	N	Y	N	-	-	Y	Y	N	Y	N	-	-	RA	Y	Y	Y	Y	N	Y
Algae toxicity (72-h)	N	-	-	RA	Y	N	Y	N	-	-	Y	N	-	-	N	-	-	RA	Y	Y	Y	Y	N	Y
HUMAN HEALTH EFFECTS																								
Acute																								
Oral LD50	Y	U	Y	N	Y	Y	Y	N	-	-	Y	Y	N	Y	N	-	-	RA	Y	Y	Y	Y	N	Y
Inhalation LC50	Y	U	Y	N	Y	N	Y	N	-	-	N	Y	N	Y	N	-	-	-	N	-	-	N	-	-
Dermal LD50	Y	U	Y	N	Y	N	Y	N	-	-	N	Y	N	Y	N	-	-	-	Y	Y	Y	N	-	-
Skin Irritation	N	-	-	N	Y	Y	Y	N	-	-	N	Y	Y	Y	N	-	-	-	Y	Y	Y	Y	N	Y
Eye Irritation	N	-	-	N	Y	N	Y	N	-	-	N	Y	N	Y	N	-	-	-	Y	Y	Y	N	-	-
Repeated Dose	N	-	-	RA	Y	Y	Y	N	-	-	Y[a]	Y	U	Y	N	-	-	RA	Y	Y	Y	Y	N	Y
Genetic toxicity *(in vitro)*	Y	N	Y	N	Y	N	Y	N	-	-	Y	Y	Y	Y	N	-	-	RA	Y	Y	Y	Y	N	Y
Genetic toxicity *(in vivo)*	Y	Y	Y	N	Y	Y	Y	N	-	-	Y	N	-	-	N	-	-	Y	N	-	-	Y	N	Y
Developmental	N	-	-	RA	Y	Y	Y	N	-	-	Y[a]	Y	N	Y	N	-	-	RA	N	-	-	Y	N	Y
Reproductive	N	-	-	RA	Y	N	Y	N	-	-	Y[a]	Y	N	Y	N	-	-	RA	N	-	-	Y	N	Y

Key: Y = Yes, N = No, U = unknown, NR = not relevant, RA = endpoint to be satisfied by read across from proposed studies for neodecanoic acid, cobalt salt
a = OECD 422 proposed

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